pain and improve joint function in patients with end-stage post-traumatic OA. This result, combined with the observation that chondroprogenitor cells are active in osteoarthritic joints, suggests that altered loading creates an environment that promotes beneficial joint remodeling.
Conclusions: Taken together, these recent advances in understanding of how mechanical forces cause loss of articular cartilage, including identification of mechanically induced mediators of cartilage loss, and of how changing joint loading can promote joint remodeling provide the basis for new biologic and mechanical approaches to the prevention and treatment of all forms of OA.

I-6
RESEARCH TOOLS FOR THE STUDY OF ASPECTS OF THE EPIGENETICS OF OSTEOARTHRITIS

I.M. Clark. *Univ. of East Anglia, Norwich, United Kingdom*

Osteoarthritis (OA) is a degenerative joint disease characterised by degradation of articular cartilage as well as thickening of the subchondral bone and the formation of osteophytes at the joint margin. The aetiology of OA is complex with genetic, developmental, biochemical and biomechanical factors contributing to the disease process. Aberrant gene expression has clearly been shown in OA and epigenetic mechanisms may contribute to this. Epigenetic modifications may include: DNA methylation, histone modifications and non-coding RNA expression (both microRNA and long non-coding RNA). A number of studies have compared epigenetic modifications in OA and normal tissues and examined epigenetic mechanisms which impact upon the disease. Key to dissecting the function of epigenetics in OA is the methodology by which these changes can be measured. This workshop will explore aspects of the research tools which can be used for the study of epigenetics in OA. It will discuss tools which are appropriate in either the culture flask, or in limiting tissue samples. The scale of the study is also important since measuring genome wide changes requires different approaches from determining a single epigenetic mark. Quantification may also be key where different technologies show degrees of accuracy or linearity which may alter conclusions or require further validation. The workshop is not a lecture on epigenetics and OA, but rather a discussion of the tools available for researchers to apply in this area and their strengths and weaknesses.

I-7
USING ZEBRAFISH TO PROBE THE GENETICS OF OSTEOARTHRITIS

L.H. Brunt †, J. Norton †, S. Reynolds †, E. Moro ‡, A. Hayes §, E. Rayfield †, C.L. Hammond †. † *Univ. of Bristol, Bristol, United Kingdom;* ‡ *Univ. of Padova, Padova, Italy;* § *Univ. of Cardiff, Cardiff, United Kingdom*

Purpose: The purpose of our work is to ascertain the extent to which zebrafish can be used as an animal model to dissect how osteoarthritis susceptibility genes affect cell behaviour in the formation and maintenance of joints.
Methods: Using BAC recombineering we have generated a number of transgenic lines in which fluorescent reporters are expressed under the control of promoters linked to cartilage biology, for example Type 2 and Type X Collagens and Gdf5, as well as reporters for the activity of a number of signalling pathways including Wnt and Hedgehog; allowing us to visualise cell behaviour in real time in the translucent fish. We have used a number of histological and immunohistochemical methods along with electron microscopy and microCT to characterise a number of events in zebrafish cartilage development, joint formation and during skeletal ageing. We have also generated Finite Element models that allow us to visualise the biomechanical strains experienced in zebrafish jaw elements resulting from the action of their associated muscles.
Results: Using a combination of techniques we show that in the zebrafish normal joint morphogenesis requires muscle action, and occurs through changes to cell organisation and orientation. We show using Finite Element Analysis that positions of high biomechanical strain in the zebrafish joint overlap regions of high Wnt signalling activity, and show that Wnt signalling is required downstream of muscle activity for correct joint morphogenesis. We also show that cartilage in ageing fish show a number structural and biochemical changes some of which are reminiscent of those seen in osteoarthritis in other animal models and in human cartilage
Conclusions: Taken together we conclude that zebrafish can be a useful animal model to dissect the role of osteoarthritis susceptibility genes in the behaviour of chondrocytes during joint development, homeostasis and ageing in normal and pathological situations.

I-8
PROTEOMICS AND BIOMARKERS IN OSTEOARTHRITIS

A.O. Aliprantis, S. Ritter. *Brigham and Women's Hosp., Boston, MA, United States*

Purpose: The application of modern proteomic techniques to disease states affords the opportunity to identify deregulated pathways that contribute to pathogenesis. These discoveries in turn may lead to new therapeutic targets, as well as "wet" biomarkers that aid in diagnosis, prognosis and the prediction of treatment responses. Building on the concept that osteoarthritis (OA) is a disease of all joint structures (synovium, cartilage and bone), and that synovial fluid (SF) may represent of synthesis of inputs from these structures, we compared the proteomic profile of knee joint SF from patients with early and late stage OA to unaffected controls by 2-dimensional gel electrophoresis and mass spectrometry. In our recent publication, using this relatively unbiased approach, 66 proteins were reported as differentially represented in healthy vs. OA SF (1). Pathway analysis identified three biologic processes among these proteins: the complement and coagulation systems and the acute phase response. Interestingly, early and late OA manifested a very similar proteomic profile. Together, these findings suggest the osteoarthritic disease processes involves activation of inflammatory pathways that are well-established by the time patients are diagnosed. This presentation will explore 1) the relative contribution of joint tissues to the SF OA proteome, including cartilage and synovium, 2) how proteomics can illuminate the pathogenesis of OA to identify therapeutic targets, 3) validation of proteomic discovery findings using multiplexed selected reaction monitoring (SRM) mass spectrometry peptide assays and 4) translation of SF protein biomarkers to quantitative serum based assays to predict disease progression in OA patients. At the end of this presentation, attendees should understand some of the major protein constituents of OA SF and how knowledge of this proteome may inform pathogenesis and biomarker development for this difficult disease.

1. Ritter SY, Subbaiah R, Bebek G, Crish J, Scanzello CR, Krastins B, Sarracino D, Lopez MF, Crow MK, Aigner T, Goldring MB, Goldring SR, Lee DM, Gobezie R, and Aliprantis AO. Proteomic analysis of synovial fluid from the osteoarthritic knee: comparison with transcriptome analyses of joint tissues. Arthritis Rheum 2013;65:981–992.

I-9
HOW LIFESTYLE FACTORS INFLUENCE THE DEVELOPMENT AND PROGRESSION OF OA

D. Dunlop. *Northwestern Univ., Chicago, IL, United States*

Purpose: Osteoarthritis (OA) is the most common worldwide disease of joints and its prevalence is growing. The worldwide obesity epidemic in older adults is fueling an increase in many chronic diseases, including osteoarthritis. This presentation will focus on knee OA, which is the most prevalent form of OA and a major cause of arthritis-related functional loss and disability.
The American College of Rheumatology 2012 recommendations recognize lifestyle factors, including weight loss and physical activity, as primary nonpharmacologic therapies for OA. Obesity has long been a recognized risk factor for the development of knee OA. Obesity contributes to OA through joint load, altered gait, and impaired muscle performance. Importantly weight influences the course of disease progression. Longitudinal cohort data provide evidence for a dose response relationship between weight change and function. Notably, 45% of adults with a weight loss $\geq$10% had a clinically meaningful improvement in WOMAC function. Randomized controlled clinical trials (RCT) support the effectiveness of weight loss to improve function in adults with knee OA. RCT evidence in obese knee OA patients demonstrated a 10% weight loss% could improve self-reported function by more than 25%.